Review

Niosomes: A Controlled and Novel Drug Delivery System

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During the past decade formulation of vesicles as a tool to improve drug delivery, has created a lot of interest amongst the scientist working in the area of drug delivery systems. Vesicular system such as liposomes, niosomes, transferosomes, pharmacosomes and ethosomes provide an alternative to improve the drug delivery. Niosomes play an important role owing to their nonionic properties, in such drug delivery system. Design and development of novel drug delivery system (NDDS) has two prerequisites. First, it should deliver the drug in accordance with a predetermined rate and second it should release therapeutically effective amount of drug at the site of action. Conventional dosage forms are unable to meet these requisites. Niosomes are essentially non-ionic surfactant based multilamellar or unilamellar vesicles in which an aqueous solution of solute is entirely enclosed by a membrane resulting from the organization of surfactant macromolecules as bilayer. Niosomes are formed on hydration of non-ionic surfactant film which eventually hydrates imbibing or encapsulating the hydrating aqueous solution. The main aim of development of niosomes is to control the release of drug in a sustained way, modification of distribution profile of drug and for targeting the drug to the specific body site. This paper deals with composition, characterization/evaluation, merits, demerits and applications of niosomes.

Key words niosome; lipid hydration method; film hydration method; nonionic surfactant; novel drug delivery system

1. INTRODUCTION

Niosomes are multilameller vesicular structure of non-ionic surfactants, similar to liposomes and are composed of non-ionic surfactant instead of phospholipids which are the components of liposomes.[1,2] So, niosome or non-ionic surfactant vesicles are now widely studied as an alternative tool to liposome. Various types of surfactants have been reported to form vesicles, and have the capacity to entrap and retain the hydrophilic and hydrophobic solute particles.[1—3]

Niosomes mainly contain two types of components *i.e.*, nonionic surfactant and the additives. The non-ionic surfactants form the vesicular layer and the additives used in niosome preparation are cholesterol and the charged molecules.[3] The presence of the steroidal system (cholesterol) improves the rigidity of the bilayer and is important component of the cell membrane and their presence in membrane affects bilayer fluidity and permeability. This carrier system protects the drug molecules from the premature degradation and inactivation due to unwanted immunological and pharmacological effects.[4]

In recent years, niosomes have been extensively studied for their potential to serve as a carrier for the delivery of drugs, antigens, hormones and other bioactive agents. Besides this, niosome has been used to solve the problem of insolubility, instability and rapid degradation of drugs.[5]

2. COMPONENTS OF NIOSOMES

Niosomes mainly contains following types of components:

2.1. Non-ionic Surfactants The non-ionic surfactants orient themselves in bilayer lattices where the polar or hydrophobic heads align facing aqueous bulk (media) while the hydrophobic head or hydrocarbon segments align in such a way that the interaction with the aqueous media would be minimized. To attain thermodynamic stability, every bilayer folds over itself as continuous membrane *i.e.* forms vesicles so that hydrocarbon/water interface remains no more exposed.[4]

Mainly following types of non-ionic surfactants are used for the formation of niosomes:

2.1.1. Alkyl Ethers L'Oreal described some surfactants[4] for the preparation of niosomes containing drugs/chemicals as

1) Surfactant-I (molecular weight (MW 473)) is C_{16} monoalkyl glycerol ether with average of three glycerol units.

2) Surfactant-II (MW 972) is diglycerol ether with average of the seven glycerol units.

3) Surfactant III (MW 393) is ester linked surfactant.

Other than alkyl glycerol, alkyl glycosides and alkyl ethers bearing polyhydroxyl head groups are also used in formulation of niosomes.[4,6,7]

2.1.2. Alkyl Esters Sorbitan esters are most preferred surfactant used for the preparation of niosomes amongst this category of surfactants.[8,9] Vesicles prepared by the polyoxyethylene sorbitan monolaurate are relatively soluble than other surfactant vesicles.[10] For example polyoxyethylene (polysorbate 60) has been utilized for encapsulation of diclofenac sodium.[11] A mixture of polyoxyethylene-10-stearyl ether : glyceryl laurate : cholesterol (27 : 15 : 57) has been used in transdermal delivery of cyclosporine-A.[4,12]

2.1.3. Alkyl Amides Alkyl amide (*e.g.* galactosides and glucosides) have been utilized to produce niosomal vesicles.[13]

2.1.4. Fatty Acid and Amino Acid Compounds Long chain fatty acids and amino acid moieties have also been used in some niosomes preparation.[14]

2.2. Cholesterol Steroids are important components of the cell membrane and their presence in membrane affect the bilayer fluidity and permeability. Cholesterol is a steroid derivative, which is mainly used for the formulation of niosomes. Although it may not show any role in the formation of bilayer, its importance in formation of niosomes and manipulation of layer characteristics can not be discarded.

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In general, incorporation of cholesterol affects properties of niosomes like membrane permeability, rigidity, encapsulation efficiency, ease of rehydration of freeze dried niosomes and their toxicity. It prevents the vesicle aggregation by the inclusion of molecules that stabilize the system against the formation of aggregates by repulsive steric or electrostatic forces that leads to the transition from the gel to the liquid phase in niosome systems. As a result of this, the niosome becomes less leaky in nature.[15)]

2.3. Charged Molecule Some charged molecules are added to niosomes to increase stability of niosomes by electrostatic repulsion which prevents coalescence. The negatively charged molecules used are diacetyl phosphate (DCP) and phosphotidic acid. Similarly, stearylamine (STR) and stearyl pyridinium chloride are the well known positively charged molecules used in niosomal preparations. These charged molecules are used mainly to prevent aggregation of niosomes.[1,16)] Only 2.5—5 mol percentage concentration of charged molecules is tolerable because high concentration can inhibit the niosome formation.[1,17)]

3. METHODS OF PREPARATION

Some important methods that are used to formulate niosomes are as follows:

3.1. Ether Injection Method In this method a solution containing a particular ratio of cholesterol and surfactant in ether is slowly injected into the preheated aqueous solution of the drugs maintained at 60 °C through the specified gauze needle. The vaporization of ether leads to the formation of unilameller vesicles of the surfactants containing drug. Alternatively, fluorinated hydrocarbons have been used as a substitute for ether for thermolabile drugs, as they vaporize at a much lower temperature. The size of niosomes obtained by this method varies between 50—1000 μm, which mainly depend on the formulation variables and experimental conditions.[4,18—20)]

3.2. Hand Shaking Method Firstly cholesterol and surfactant are dissolved in some organic solvent (like ether, chloroform, benzene *etc.*). Thereafter, solvent is evaporated under reduced pressure in a vacuum evaporator in a round bottom flask which then leaves the mixture of solid surfactant and cholesterols on the walls of round bottom flask. This layer was then rehydrated with aqueous solution containing drug with continuous shaking which results in swelling of surfactant layer. Swelled amphiphiles eventually folds and form vesicles which entrap the drugs. The liquid volume entrapped in vesicles was found to be small *i.e.* 5—10%.[4,18,19)]

3.3. Sonication Method In this method at first the surfactant-cholesterol mixture is dispersed in the aqueous phase. This dispersion is then probe sonicated for 10 min at 60 °C, which leads to the formation of multilameller vesicles (MLV). These MLVs are further ultrasonicated either by probe sonicator or bath sonicator, which in turn leads to the formation of unilameller vesicles.[4,18)]

3.4. Reverse Phase Evaporation Method In this method the solution of cholesterol and surfactant is prepared in a mixture of ether and chloroform (1 : 1). To this, the aqueous solution of drug is added and sonicated at temperature 4—5 °C. The solution thus obtained is further sonicated after addition of phosphate buffer saline (PBS) resulting in the formation of gel. Thereafter temperature is raised to 40 °C and pressure is reduced for the removal of solvent. The PBS is added again and heated on water bath at 60 °C for 10 min to yield niosomes.[4,21)]

3.5. Transmembrane pH Gradient (Inside Acidic) Drug Uptake Process (Remote Loading) According to this principle, the interior of niosome has the lower pH value (acidic pH) than the outer side. The added unionized basic drug crosses the niosome membrane but after entering into the niosome it gets ionized in acidic medium and is unable to leave the niosome and thus this method increases the entrapment efficiency of such drugs. The acidic pH towards the interior of niosomes acts as an intravesicular trap for the drugs.[22)]

3.6. Extrusion Method In this method, a mixture of cholesterol and diacetyl phosphate is prepared and then solvent is evaporated using rotary vacuum evaporator to leave a thin film. The film is then hydrated with aqueous drug solution and the suspension thus obtained is extruded through the polycarbonate membrane (mean pore size 0.1 μm) and then placed in series up to eight passages to obtain uniform size niosomes.[23,24)]

3.7. Microfluidization Method In this method two fluidized streams (one containing drug and the other surfactant) interact at ultra high velocity, in precisely defined micro channels within the interaction chamber in such a way that the energy supplied to the system remains in the area of niosomes formations. This is called submerged jet principle. It results in better uniformity, smaller size and reproducibility in the formulation of niosomes.[23,24)]

4. TYPES OF NIOSOMES

4.1. Bola Surfactant Containing Niosomes Bola surfactant containing niosomes are the surfactants that are made of omega-hexadecyl-bis-(1-aza-18 crown-6) (bola surfactant): span-80/cholesterol in 2 : 3 : 1 molar ratio.[3,21)]

4.2. Proniosomes Proniosomes are the niosomal formulation containing carrier and surfactant, which requires to be hydrated before being used. The hydration results in the formation of aqueous niosome dispersion. Proniosomes decreases the aggregation, leaking and fusion problem associated with niosomal formulation.[25)]

carrier + surfactant = proniosomes

proniosomes + water = niosomes

4.3. Aspasomes Combination of acorbyl palmitate, cholesterol and highly charged lipid diacetyl phosphate leads to the formation of vesicles called aspasomes.[26)] Aspasomes are first hydrated with water/aqueous solution and then sonicated to obtain the niosomes. Aspasomes can be used to increase the transdermal permeation of drugs. Aspasomes have also been used to decrease disorder caused by reactive oxygen species as it has inherent antioxidant property.[26)]

aspasomes

↓

hydration by aqueous solution

↓

sonication

↓

niosomes

4.4. Niosomes in Carbopol Gel Niosomes were prepared using drug, spans and cholesterol. The niosomes thus obtained were then incorporated in carbopol-934 gel (1% w/w) base containing propylene glycol (10% w/w) and glycerol (30% w/w). Using human cadaver skin, *in vitro* diffusion studies of such niosomal gel, plain drug gel and marketed gel were carried out in diffusion cell. It was observed that the mean flux value and diffusion co-efficient were 5 to 7 times lower for niosomal gel as compared to plain drug gels. Moreover, carrageenan induced paw edema inhibition (*i.e.* 66.68±5.19%) was higher by niosome formulation as compared to plain gel.[22,27)]

4.5. Vesicles in Water and Oil System (v/w/o) It has been reported that the emulsification of an aqueous niosomes into an oil phase form vesicle in water in oil emulsion (v/w/o).[9,22)] This can be prepared by addition of niosomes suspension formulated from mixture of sorbitol monostearate, cholesterol and solulan C24 (poly-24-oxyethylene cholesteryl ether) to oil phase at 60 °C. This results in the formation of vesicle in water in oil (v/w/o) emulsion which by cooling to room temperature forms vesicle in water in oil gel (v/w/o gel).[22)] The v/w/o gel thus obtained can entrap proteins/proteinous drugs and also protect it from enzymatic degradation after oral administration and controlled release. The immunogenic properties of v/w/o gel and w/o gel reported that both exhibit immunoadjuvant tendency. In this system aqueous niosomes (v/w) are emulsified into the oily phase.

4.6. Niosomes of Hydroxyl Propyl Methyl Cellulose In this type, a base containing 10% glycerin of hydroxy propyl methyl cellulose was first prepared and then niosomes were incorporated in it.

The bioavailability and reduction of paw edema induced by carrageenan was found to be higher by this niosomal system than the plain formulation of flurbiprofen.[8,22)]

5. FACTOR AFFECTING THE PHYSICOCHEMICAL PROPERTIES OF NIOSOMES

5.1. Membrane Additives Stability of niosomes can be increased by the number of additives into niosomal formulation along with surfactant and drugs. The membrane stability, morphology and permeability of vesicles are affected by numbers of additives *e.g.* addition of cholesterol in niosomal system increases the rigidity and decreases the drugs permeability through the membrane.[28)] Niosomes prepared by C16G2/cholesterol/M-polyethylene glycol (PEG)-Chol show spherical vesicles with diameters ranging from 20 to 200 nm.[22,29)]

5.2. Temperature of Hydration Shape and size of niosome is also influenced by the hydration temperature. Assembly of the niosomes vesicles is affected by the temperature change of niosomal system. Temperature change can also induce the vesicle shape transformation. Polyhydral vesicles of $C_{16}G_2$: solulan C_{24} (91 : 9) is formed at 25 °C, but it is converted into spherical vesicles at 45 °C and on cooling from 55 to 49 °C, the vesicles produced a cluster of smaller spherical niosomes.[16,22,30)]

5.3. Properties of Drugs The drug entrapment in niosomes is affected by molecular weight, chemical structure, hydrophilicity, lipophilicity as well as the hydrophilic lipophilic balance (HLB) value of the drug.[15)] Vesicle size may increase due to entrapment of drug. Drug particle interact with the surfactant head groups, which may increase charge on polymer and thus cause repulsion of the surfactant bilayer which leads to increase in vesicle size.[22,28,31)]

5.4. Amount and Type of Surfactant As the HLB value of surfactants like span 85 (HLB 1.8) to span 20 (HLB 8.6) increased, the mean size of niosomes also increases proportionally. It is due to the fact that surface free energy decreases with increase in hydrophilicity of surfactant. Alkyl chain is present in well ordered structure in gel state, while in the liquid state the structure of bilayer is more disordered. The gel–liquid phase transition temperature (TC) is used for characterization of surfactant and lipids. Entrapment efficiency is also affected by phase transition temperature *i.e.* span 60 having higher TC, provide better entrapment efficiency. Entrapment efficiency of the niosomes is affected by the HLB value for *e.g.* niosomes have high entrapment efficiency at HLB value 8.6 but HLB value 14 to 17 is not suitable for niosomes formulation.[9,22,27)]

5.5. Cholesterol Content and Charge on the Surfactant Hydrodynamic diameter and entrapment efficiency were found to be increased due to cholesterol content in the niosomal bilayer.[32)] Cholesterol can act by two ways. First, it can increase the chain order of liquidated bilayer and second, by decreasing the chain order of the gel state bilayer,[32)] cholesterol affects the hydrodynamic diameter and entrapment efficiency. It has been reported that release rate of drug decreases and rigidity of bilayer increases due to high concentration of cholesterol.[32—34)]

5.6. Structure of Surfactants The geometry of the vesicles formed during the niosomal preparation also depends upon the critical packing parameter (CPP). According to CPP the geometry of the vesicles can be predicted.[27)] CPP can be calculated using following equation[35)]:

$$\text{critical packing parameter (CPP)} = \frac{v}{lc \times a_0}$$

where

v=hydrophobic group volume,

lc=the critical hydrophobic group length,

a_0=the area of hydrophilic head group

CPP is helpful in predicting the structure of niosome vesicles in following way;

spherical micelles formed if CPP$<$1/2

bilayer micelles is formed if 1/2$<$CPP$<$1

inverted micelles is formed if CPP$>$1.

5.7. Method of Preparation Method of preparations can also affect the niosomal properties. Different type of methods like ether injection, hand shaking; sonication *etc.* has been reviewed by Khandare *et al.*[23)] The average size of acyclovir niosomes prepared by hand-shaking process was larger (2.7 μm) as compared to the average size of niosomes 1.5 μm prepared by ether injection method which may be attributed to the passage of cholesterol and span-80 solution through an orifice into the drug solution.[19)]

Reverse phase evaporation can be used to produce smaller size vesicles. Vesicles with smaller size and greater stability can be produced by microfluidization method. Niosomes obtained by transmembrane pH gradient (inside acidic) drug uptake process showed greater entrapment efficiency and

better retention of drug.[36)]

5.8. Resistance to Osmotic Stress Diameter of niosomal vesicles was found to be decreased when niosomal suspension is kept in contact with hypertonic salt solution.

There is slow release with slight swelling of vesicles, which is due to inhibition eluting fluids from vesicles, followed by faster release, which may be due to decrease in mechanical strength under osmotic stress.[6,24,37)]

Volume of hydration medium and time of hydration of niosomes are also critical factors which affects the niosomal assembly along with the above mentioned factors. Improper selection of these factors may result in formation of fragile niosomes or creation of drug leakage problems.[22)]

6. ADVANTAGES ASSOCIATED WITH NIOSOMES

The niosomes as a drug delivery system offer the following advantages:

1) Niosomes have better patient compliance and better therapeutic effect than conventional oily formulations.[38)]

2) Niosomes can be utilized in the delivery of wide variety of drugs as it has capability to entrap hydrophilic, lipophilic as well as amphiphilic drugs.[39,40)]

3) Niosomes show controlled and sustained release of drugs due to depot formation.[32,41)]

4) Shape, size, composition, fluidity of niosomes drug can be controlled as and when required.[41)]

5) Niosomes show a greater bioavailability than conventional dosage forms.[40)]

6) Niosomes had been effectively used in targeting drugs to various organs.[42)]

7) Niosomes are more stable than liposomes.[22)]

8) Niosomes can increase the permeation of drugs through the skin.[43)]

9) Niosomes can be administrated *via* various routes like oral, parenteral and topical *etc.*[24)]

10) Niosomes are biodegradable, biocompatible and non immunogenic to the body.[24)]

11) Handling, storage and transportation of the niosomes is easy.[38)]

12) Oral bioavailability of the drug can be improved using niosome.[44)]

13) It can protect the drugs from biological enzymes and acid thereby increasing the stability of the drugs.[38)]

14) No tissue irritation and damage are caused by penetration enhancers in the ocular drug delivery system.[38)]

6.1. Liposome *versus* Niosome The differences between liposomes and niosomes are described in Table 1.[24)]

6.2. Similarities between Liposome and Niosome[21)]

1) The liposomes and niosomes are functionally same.

2) Both can be used in targeted and sustained drug delivery system.

3) Property of both depends upon composition of the bilayer and methods of their preparation.

4) Both increase bioavailability and decrease the body clearance.

7. CHARACTERIZATIONS OF NIOSOMES

7.1. Entrapment Efficiency (EE) It is defined as the percentage amount of drug which is entrapped by the niosome.[22)] Entrapment efficiency is calculated by using the formula:

$$\mathrm{EE} = \frac{\text{amount of entrapped drug}}{\text{total amount added}} \times 100$$

For the determination of entrapment efficiency, the un-entrapped drug is first separated using suitable method (*e.g.* by centrifugation method). The resulting solution is then separated and supernatant liquid is collected. The collected supernatant is then diluted as specified and estimated using appropriate method as described in monograph of that particular drug.[7,16,45)]

Both the entrapment efficiency (EE) and yield of niosome depend on the method of preparation as well as physicochemical properties of drug. The number of double layers, vesicle size and its distribution, entrapment efficiency of the aqueous phase, and the permeability of vesicle membranes are influenced by the methodology used for formulation as well as the addition of cholesterol as they make the niosomes less leaky.[15)] Bhaskaran and Lakshmi reported that transmembrane pH gradient method had higher EE with respect to other processes like ether injection method and film hydration method. In this process the presence of a net charge, whether negative or positive can increase water uptake within the double layer.[46)]

Such hydration leads to an increase with respect to uncharged vesicles of loaded hydrophilic molecules that can probably be located within the bilayer as well as in the core of the aggregated structures.

7.2. Size, Shape and Morphology

7.2.1. Transmission Electron Microscopy (TEM) TEM is used to determine the size, shape and lamellarity of niosome. In brief, a suspension is prepared and mixed with 1% phosphotungstic acid (in sufficient amount). A drop of resultant was then used on carbon coated grid, draining off the excess and then the grid was observed and images are taken under suitable magnification under TEM after complete drying (Philips TEM).[1,7)]

7.2.2. Freeze Fractured Microscopy The size and shape of niosome were found to be dependent on the drug entrapment, nature of drug used and the nature of surfactant. For the determination of size, vesicles are generally freeze thawed and then visualized under freeze fractured electron

Table 1. Differences between Liposomes and Niosomes

Liposomes	Niosomes
• More expensive	• Less expensive
• Phospholipids are prone to oxidative degradation	• But non-ionic surfactants are stable toward this
• Required special method for storage, handling and purification of phospholipids	• No special methods are required for such formulations comparatively
• Phospholipids may be neutral or charged	• Non-ionic surfactants are uncharged

microscope. Liquid propane is generally used for the cryofixation of the vesicular suspension (glycol may be used as cryoprotectant) at low pressure (10^{-2} Pa). The cryofixed vesicles are fractured at a specified angle. The resultant surface is then shadowed using platinum or carbon vapors at an angle of 45°. Carbon coating used in this method strengthens the formed replica. Replica is cleaned and then observed and examined using TEM.[4)]

7.2.3. Optical Microscopy Technique This technique is also used for observation of niosome size and shape. Nearly 100 niosome are used for particle size determination. In this method size of stage micrometer coinciding with the eye piece micrometer is recorded and size of niosome is then calculated.[47)]

Nowadays laser beam based mastersizer is used for the determination size distribution, mean surface diameter and mass distribution of niosome.[4)] Dynamic light scattering (DLS) analysis using Malvern Zeta Sizer is also used for the determination of size distribution, mean diameter and zeta potential.

7.3. *In Vitro* Release Study In this study dialysis membrane method is generally used. In this method small amount of niosomes are taken into dialysis bag and are tied at both the ends. Another beaker containing suitable dissolution media is maintained at 37 °C and the dialysis bag is put into it and stirred by a magnetic stirrer. A sample solution is taken from the beaker at specified time intervals and replaced with fresh dissolution media. The samples were analyzed for the concentration of drug at specified wave length reported in respective monograph of that particular drug.[46)]

7.4. Tissue Distribution/*In Vivo* Study Tissue distribution profile has been studied using suitable animal models. Bhaskaran and Lakshmi, used three groups of healthy albino rats (100—150 gm) for tissue distribution profile, each group contain three animals (3×3=9). The first group was treated as control in which free niosome without drug were injected, to the second group free drug was injected. The third group was treated by lyophilized niosome. After sacrificing the animals, various tissue like liver, lungs, spleen, kidney and heart were removed. After washing the tissue with phosphate buffer (pH 7.4) the organs were homogenized and centrifuged. The supernatant thus obtained was used for the determination of drug content using suitable method.[46)] Similarly, Jadon *et al.*[45)] used male albino rats for this study. After administration of the free drug and drug entrapped in niosomes, the amount of drug in plasma was determined. The animals were divided into three groups, each group contains five animals. First group was treated as control and was injected with PBS (pH 7.4), the second and third groups were treated with the pure drug and niosomes containing drug respectively by oral route, after predetermined time intervals, blood samples were collected, centrifuged and frozen immediately and then analyzed using HPLC.[45,47)]

7.5. Stability Study Stability studies are done by storing niosome at two different conditions, usually 4±1 °C and 25±2 °C. Formulation size, shape and number of vesicles per cubic mm can be assessed before and after storing for 30 d. After 15 and 30 d, residual drug can also be measured. Light microscope is used for determination of size of vesicles and the numbers of vesicles per cubic mm is measured by haemocytometer.[7,46)]

$$\text{number of niosomes per cubic mm} = \frac{\text{total number of niosomes} \times \text{dilution factor}}{\text{total number of small squares counted}} \times 400$$

7.6. Number of Lamellae NMR spectroscopy, small angle X-ray spectroscopy and electron microscopy has been utilized for determination of number of lamellae.[22,48)]

7.7. Membrane Rigidity The mobility of fluorescence probe as a function of temperature has been used for the determination of membrane rigidity of some niosomal formulations.[22,49)]

7.8. Vesicular Surface Charge Niosomes are generally prepared by the inclusion of charged molecules in bilayer to prevent the aggregation of vesicles.[41)] A reduction in aggregate formation was observed when charged molecule like dicetyl phosphate was incorporated in vesicles.[50)] The charge on vesicles is expressed in terms of zeta potential and calculated using the Henry's equation.[4,49)]

$$£ = \mu E \pi \eta / \Sigma$$

where,
£: Zeta potential
μE: Electrophoretic mobility
η: Viscosity of medium
Σ: Dielectric constant

8. APPLICATIONS OF NIOSOMES

The applications of niosomes can be mainly classified into three categories and have been summarized in Table 2.

8.1. To Improve the Stability and Physical Properties of the Drugs

8.1.1. To Increase Oral Bioavailability It has been reported that with the formulation of niosomes, the oral bioavailability of the acyclovir as well as griseofulvin was increased as compared to the drug alone. Similarly, the absorptivity of poorly absorbed peptide and ergot alkaloid can be increased by the administration in the bile duct of rats when administered as micellar solution together with the POE-24-cholesteryl ester.[40,45)]

8.1.2. To Modify the Physicochemical Properties of Drugs It is studied that non ionic surfactant can be used to improve the physicochemical properties of drug free niosomes as well as drug loaded niosomes.[24,50)]

8.1.3. For Improvement of Stability of Peptide Drugs The stability of peptide drugs can be increased significantly by using niosomes *e.g.* 8-arginin vasopressin, 9-glycinamide-ω *etc.*[33)] Also, the *in vitro* release of insulin from niosomes formulated by span 40 and span 60 in simulated intestinal fluid was lower than the niosomes formulated by span 20 and span 80. Niosomes prepared by the span 60 has high resistance against proteolytic enzyme and exhibit good stability in storage temperature and in presence of sodium deoxycholate.[51)]

8.1.4. To Promote Transdermal Delivery of Drugs Many drugs such as lidocaine, estradiol, cyclosporine *etc.* are used for topical and transdermal drug delivery system by formulating them as niosomes.[16,52,53)] The niosomes of natural compound, ammonium glycyrrhizinate were formulated for effective anti-inflammatory activity using new non-ionic surfactant, $\alpha,\acute{\omega}$-hexadecyl-bis-(1-aza-18-crown-6) (bola surfac-

Table 2. Applications of Niosomes

S. No.	Application	Components	Method used	Drug used	References
1	As a drug delivery carrier	α,ω-Hexadecyl-bis-(1-aza)18-crown-6(bola), Span 80, Cholesterol	Thin layer evaporation technique	5-Fluorouracil (5-FU)	2)
2	To increase bioavailability	Cholesterol, Sorbitan monosrearate (span 60), Dicetylphosphare (DCP)	Film hydration method	Acyclovir	40)
		Span 20, Span 40, Span 60, Cholesterol, DCP	Thin film method, Ether injection method	Griseofulvin	45)
3	For brain targeting	*N*-Palmitoyl glucosamine (NPG), Span 60, Cholesterol, Solulan C24	Probe sonication method	Vasoactive Intestinal Peptide (VIP)	59)
4	To prolong the release time	Sorbitan esters	Reverse phase evaporation method	Rifampacin	66)
5	For drug targeting	Palmitic acid *N*-Hydroxysuccinimide, Glucosamine, Sorbitan monostearate (Span 60),	Sonication method	Transferrin	59)
		Cholesterol, Glycol chitosan Sorbitan monostearate (span 60)	Reverse phase evaporation method	Methotrexate	67)
6	In leishmaniasis	Span 40, Cholesterol, DCP	Solvent evaporation method	14-deoxy-11-oxoandograph-olide	68)
		Span 20, Cholesterol, Phosphotidic acid	Mechanical shaking method without sonication	Amarogentin	9)
7	For anti inflammatory effect	Cholesterol (CH), Dicetyl phosphate (DCP) and Surfactants (Tween 85, Pluronic F108)	Reverse phase evaporation method	Diclofenac sodium	69)
8	In anticancer therapy	C_{16} Monoalkyl glycerol ether	Sonication method	Doxorubicin	10)
		Span 60, Cholesterol, DCP	Lipid layer hydration method	Bleomycin	70,71)
		Span 20, Span 60, Span 40, Tween 20, Tween60, Brij 76, Brij 78, Brij 72	Thin layer hydration method	Paclitaxel	72)
		Span 40, Cholesterol	Transmembrane pH gradient (inside acidic) drug uptake process (remote loading method)	Vincristine	38)
9	In localized psoriasis	Chitosan	Lipid layer hydration method	Methotrexate	60)
		Phosphotidyl choline, Span 60, Cremophor RH40, Cholesterol, Butylated hydroxy toluene	Thin film hydration method	Dithranol	73)
10	In oral delivery of peptide drug	Brij 52, Brij72, Brij92, Brij76, Brij97, Brij58, Brij35, DCP, Cholesterol	Film hydration method	Insulin	74)
11	In diagnostic imaging	*N*-Palmitoyl-glucosamine (NPG), Polyethylene glycol (PEG)-4400	Ether injection method	Gadobenate	59,63)
12	In transdermal drug delivery system	α,ω-Hexadecyl-bis-(1-aza)18-crown-6(bola), Span 80, Cholesterol	Film hydration method	Ammonium glycyrrhiinate	3)
		Brij 96, Cholesterol	Sonication method	Estradiol	75)
13	In opthalamic drug delivery system	Polyoxyethylene 20 sorbitan monostearate (Tween 60), Polyoxyethylene 20 sorb-itan monooleate (Tween 80), Polyoxyethylene 23 Lauryl-ether, Cholesterol, DCP	Thin film hydration technique	Gentamicin sulphate	57)
		Chitosan, Carbopol	Reverse-phase evaporation (REV) technique	Timolol meleate	76)
		Span 20, Span 60, Cholesterol	Reverse phase evaporation method, Thin layer hydration method	Acetazolamide	58)
14	For lung targeting	Span 85, Cholesterol	Hand shaking method, Ether injection method	Rifampicin	77)
15	In thromboembolic disease	Hexadecyl poly(3)glycerol, DCP, Cholesterol	Film method	Urokinase	78)
16	For stability improvement	Span 60, Cholesterol	Ether injection method	Fluconazole	79)

Table 2. (Continued).

S. No.	Application	Components	Method used	Drug used	References
17	To increase immune response and immunological selectivity	Dimethyldioctadecylamm onium bromide (DDA) and α,α'-trehalose-6,6′-dibehenate (TDB), 1-Monopalmitoyl glycerol (MP), Cholersterol	Dehydration–rehydration method	Ag85B-ESAT-6, MSP1 or GLURP	[80]
18	For sustained antiplatelet effect	Cholesterol, Tween 60, Stearylamine	Lipid hydration method	Indomethacin	[81]
19	For liver targeting	Span 60, Cholesterol, DCP	Thin film hydration method	Ribavirin	[82]
20	For enhancement of therapeutic index	Span and Tween (20 and/or 60), Cholesterol	Reverse phase evaporation method	α-Lipoic acid	[83]
21	To increase entrapment efficiency	Span 60, Cholesterol, DCP	Thin film hydration method	Ketoprofen	[84]
22	To reduce toxicity	Span 20, Span 40, Span 60, Cholesterol	Thin film hydration method	Cefpodoxime Proxertil	[85]

tant)–span 80 cholesterol (2 : 3 : 1 ratio). It was observed that bola surfactant increased the intracellular delivery. Experimental study showed that the bola niosomes were able to promote the intracellular uptake of ammonium glycerrhizinic acid.[3]

8.1.5. As a Tool for Improvement of Stability of Immunological Products The niosomes can be used as an important tool for immunological selectivity, low toxicity and more stability of the incorporated active moiety.[24,54]

8.1.6. To Improve Anti-inflammatory Activity Niosomal formulation of diclofenac sodium prepared with 70% cholesterol showed greater anti-inflammatory effect as compared to the free drug.[55] Similarly, nimesulide and flurbiprofen showed greater activity than the free drug.[27]

8.2. For Controlled Release of Drugs

8.2.1. To Prolong the Release Rate The release rate of drugs like withaferin and gliclazide from the niosomes was found slower as compared to withaferin without incorporating in niosomes.[56]

8.2.2. In Ophthalamic Drug Delivery Experimental results of the water soluble antibiotic gentamicin sulphate showed a substantial change in the release rate. Beside this, the percent entrapment efficiency of gentamicin sulphate was altered when administered as niosomes. Also, as compared to normal drug solution, niosomes of drug show slow release.[57] Niosomal formulation containing timolol meleate (0.25%) prepared by chitosan coating exhibited more effect on intra ocular tension with fewer side effects as compared to the marketed formulation.[58]

8.3. For Targeting and Retention of Drug in Blood Circulation

8.3.1. For Increased Uptake by A431 Cells For targeting purpose, chitosan based vesicles incorporating transferrin and glucose as ligand have been reported.[59] These vesicles bind CoA (co-A) to their surface. Chitosan containing vesicles are then taken up by A431 cells and the uptake was found to be enhanced by transferrin.[59]

8.3.2. For Liver Targeting Methotrexate was reported to be selectively taken up by liver cells after administration as a niosomal drug delivery system.[42]

8.3.3. To Improve the Efficacy of Drugs in Cancer Therapy Niosomes can also be used as a suitable delivery system for the administration of drugs like 5-FU, an anticancer drug. PEG coated niosomes (based on bola-surfactant) have been utilized as a drug carrier and an improved drug penetration of 8- and 4-folds with respect to a drug aqueous solution and to a mixture of empty bola-niosomes with a drug aqueous solution has been reported.[2] Niosomes of doxorubicin prepared from C_{16} monoalkyl glycerol ether with or without cholesterol, exhibited an increased level of doxorubicin in tumor cells, serum and lungs, but not in liver and spleen.[10] Higher area under curve (*AUC*) has been found to be exhibited by niosomal formulation of methotrexate as compared to methotrexate solution which was administered either orally or intravenously. Niosomal preparation of methotrexate exhibited greater antitumor activity as compared to plain drug solution.[42] Similarly, by incorporating withaferin in niosomes, it showed an improved therapeutic activity because of the extended drug release.[56]

8.3.4. In Treatment of Localized Psoriasis Methotrexate, a drug used in psoriasis has limited applications due to its formulation problem. In the treatment of localized psoriasis, niosomes of methotrexate taking chitosan as polymer have shown promising results.[60]

8.3.5. In Leismaniasis The leismaniasis parasite mainly infects liver and spleen cells. The commonly used drugs, antimonials, may damage the body organ like heart, liver, kidney *etc.* The efficiency of sodium stibogluconate has been found to be enhanced by incorporation in niosomes.[9] The additive effect was observed for two doses given on successive days. Moreover, the distribution of antimony in mice showed the higher level of antimony in liver after its intravenous (i.v.) administration *via* niosomes drug formulation.[24,61]

8.3.6. In Diagnostic Imaging It has been studied that niosomes can also act as a carrier radiopharmaceuticals and showed site specificity for spleen and liver for their imaging studies using ^{99m}Tc labeled DTPA containing niosomes.[62] Conjugated niosomal formulations of gadobenate with (*N*-palmitoyl-glucosamine, NPG), PEG 4400 and both PEG and NPG can be used to increased tumor targeting of a paramagnetic agent.[63]

8.3.7. Carrier for Haemoglobin Niosomes play an important role as a carrier for haemoglobin. The niosomal haemoglobin suspension was found to give superimposable curve on free haemoglobin curve.[64,65]

9. CONCLUSION

Niosomes drug delivery system is an efficient approach towards novel drug delivery. Niosomes are composed mainly of non-ionic surfactants and cholesterol. Niosomes may be prepared by various methods like ether injection method, hand shaking method, sonication method, reverse phase evaporation method, remote loading method, extrusion method and microfluidization method. The properties of niosomes are affected by additives, methods of preparation, drug properties, amount, structure and type of surfactant used, cholesterol content and resistance to osmotic stress. In nutshell, as a drug delivery device, compared to liposomes, niosomes are osmotically active and are quite stable chemically by their own as well as improve the stability of the drug so entrapped and delivered. They do not require special conditions for handling, protection or storage and industrial manufacturing. Beside this, they offer flexibility in structural characteristics (composition, fluidity, size), and can be designed as desired. Niosomes offer various advantages over other drug delivery devices and have found applicability in pharmaceutical field. It was thus concluded that niosomes are very effective drug delivery tools for incorporation/targeting of various therapeutically active moieties and the onus lies on future scientists to effectively harness its potential in diverse application areas for the benefit of mankind.

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